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(54) **EPIGENETIC METHOD FOR THE IDENTIFICATION OF SUBPOPULATIONS OF CD8+ T LYMPHOCYTES, IN PARTICULAR CD8 ALPHA AND BETA T LYMPHOCYTES**

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C12Q 1/68 (2018.01)
C12Q 1/6886 (2018.01)
C12Q 1/6881 (2018.01)

(52) **U.S. Cl.**
CPC ***C12Q 1/6886*** (2013.01); ***C12Q 1/6881*** (2013.01); *C12Q 2600/154* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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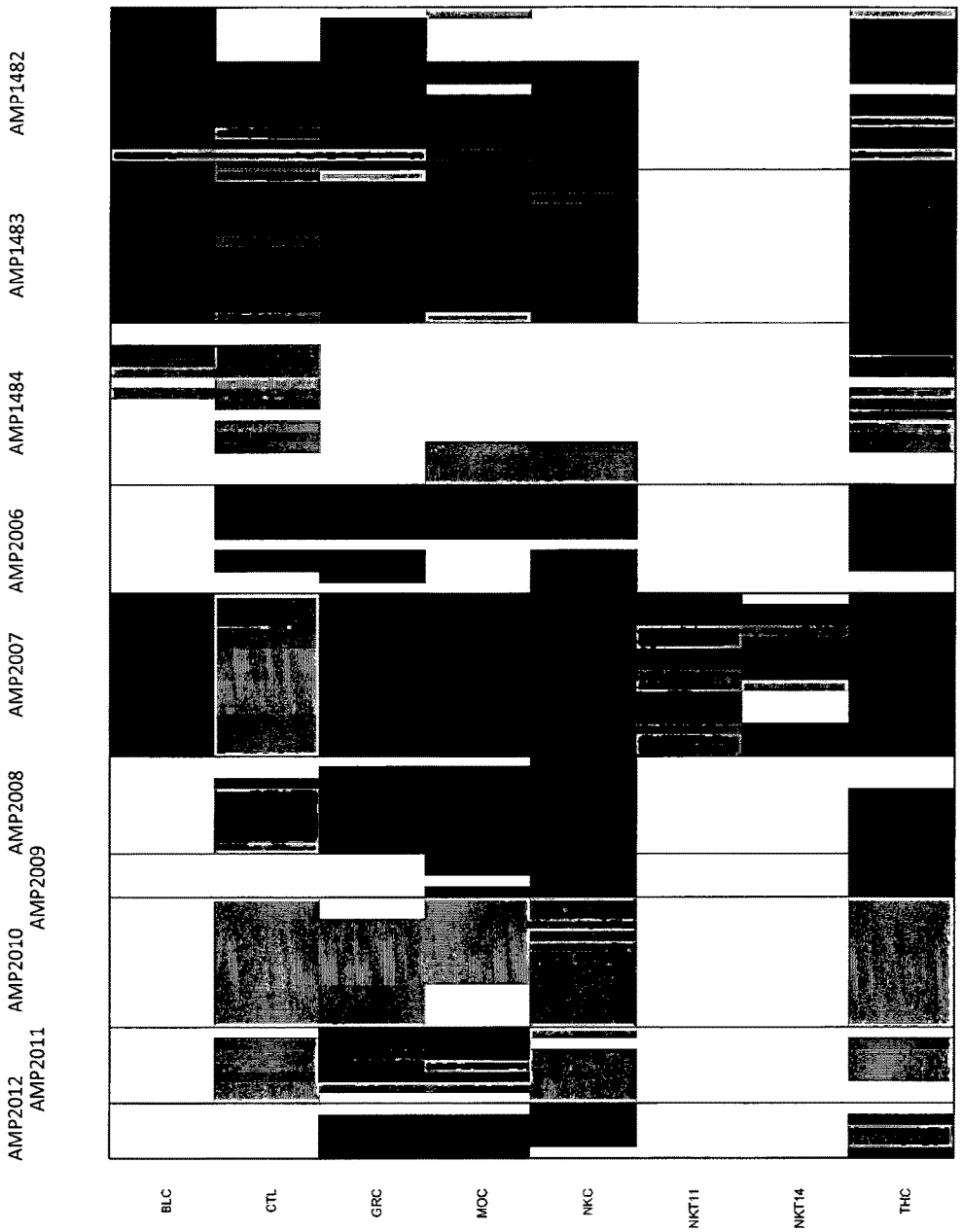
(57) **ABSTRACT**

The present invention relates to a method, in particular an in vitro method, for identifying CD8 positive subpopulations of a mammal, wherein said method comprises analyzing the bisulfite convertibility of at least one CpG position in the CD8 beta and CD8 alpha cell specific bisulfite convertibility gene region according to SEQ ID No. 1 and 2, wherein a bisulfite convertibility of at least one CpG position in said gene regions is indicative for a CD3+CD8+ and/or CD3+/−CD8+ cell. The analyzes according to the invention can identify CD3+CD8+ and/or CD3+/−CD8+ cells on an epigenetic level and distinguish them from all other cells in complex samples, such as, for example, other blood cells.

20 Claims, 4 Drawing Sheets

Specification includes a Sequence Listing.

Figure 1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AMP1484
AMP2006
AMP2007
AMP2008
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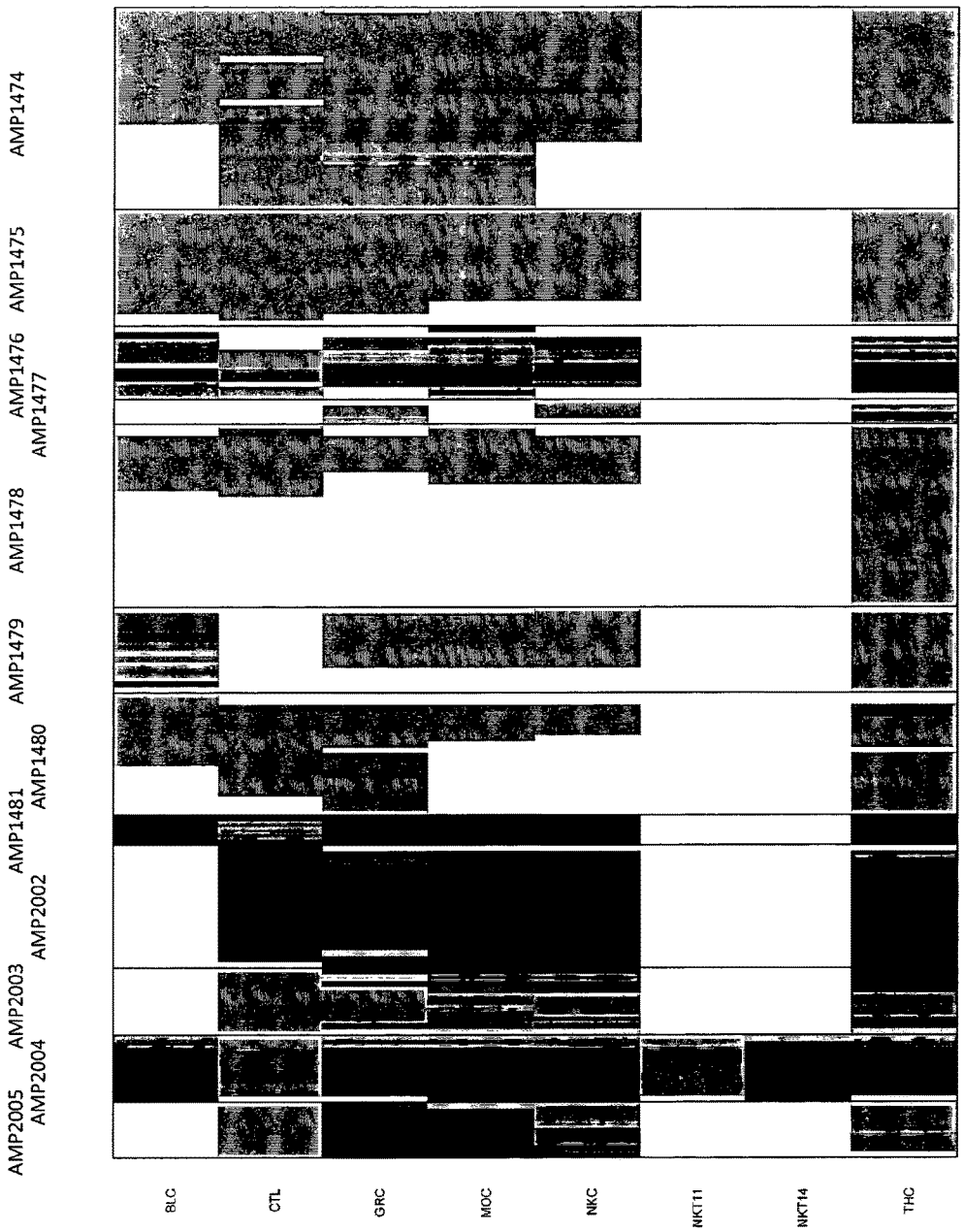
AMP2010
AMP2011
AMP2012
BLC
CTL
GRC
MOC
NKC
NKT11
NKT14
THC

Figure 2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AMP1478
AMP1479
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NKC
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THC

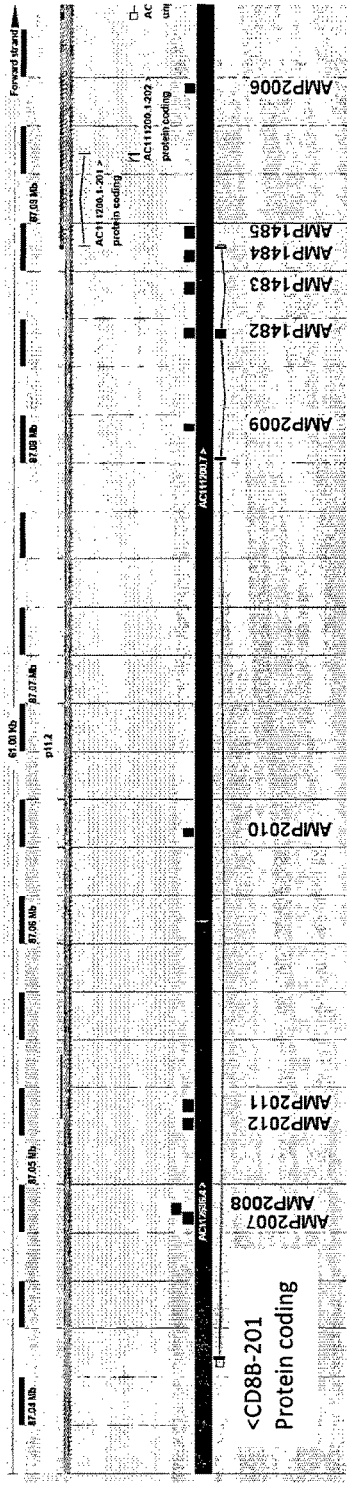

Figure 3

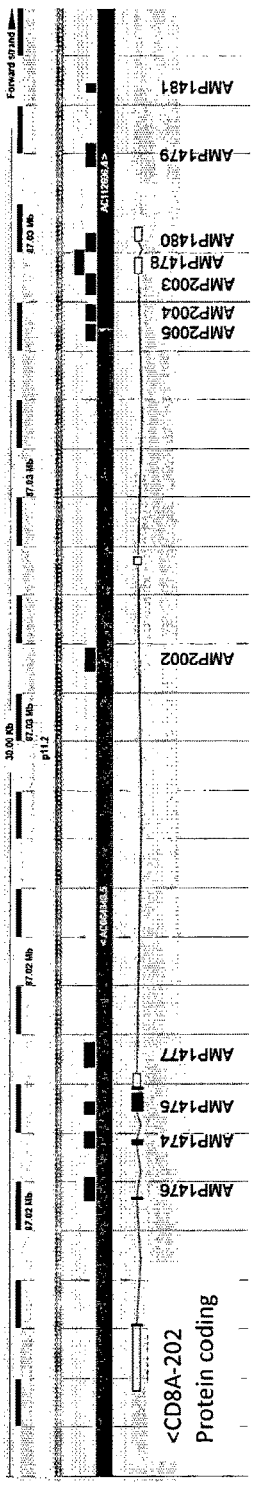

Figure 4

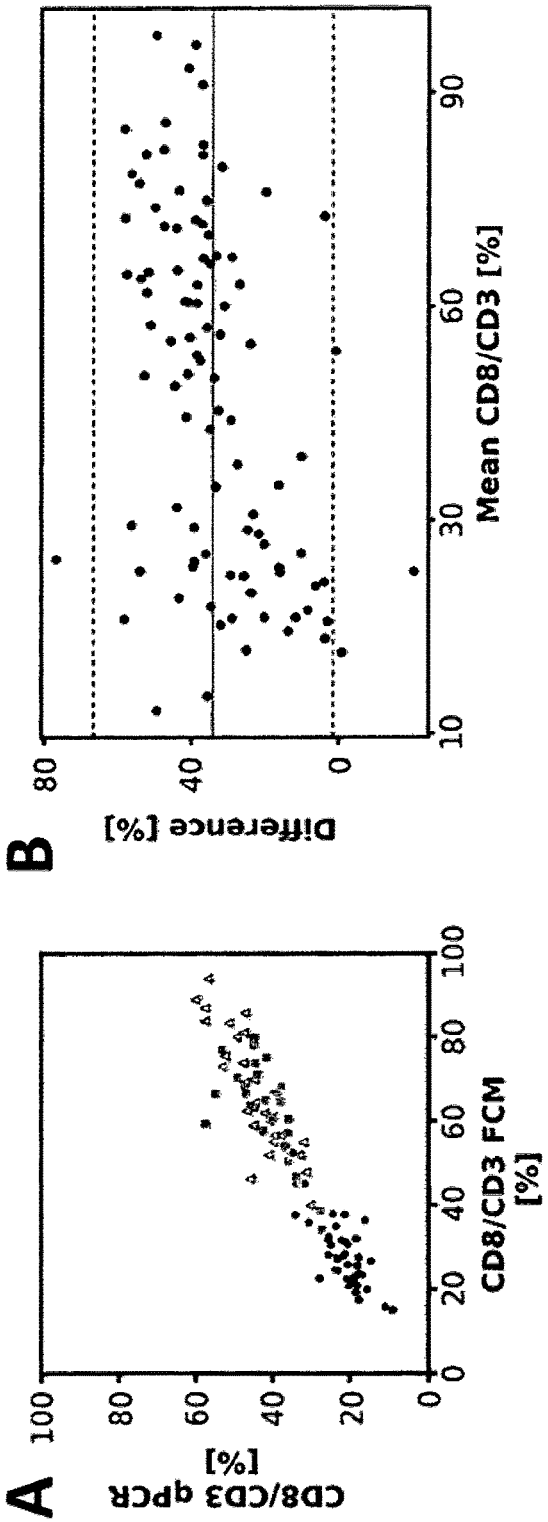
A
CD8/CD3 qPCR [%]
CD8/CD3 FCM [%]
0
20
40
60
80
100
B
Difference [%]
Mean CD8/CD3 [%]
10
30
60
90

Figure 5

EPIGENETIC METHOD FOR THE IDENTIFICATION OF SUBPOPULATIONS OF CD8+ T LYMPHOCYTES, IN PARTICULAR CD8 ALPHA AND BETA T LYMPHOCYTES

CROSS REFERENCE TO A RELATED APPLICATION

This application is a National Stage Application of International Application Number PCT/EP2013/074642, filed Nov. 25, 2013; which claims priority to Great Britain Application No. 1221133.0, filed Nov. 23, 2012; both of which are incorporated herein by reference in their entirety.

The Sequence Listing for this application is labeled "SeqList-15May15.txt", which was created on May 15, 2015, and is 116 KB. The entire content is incorporated herein by reference in its entirety.

The present invention relates to a method, in particular an in vitro method, for identifying CD8 positive subpopulations of a mammal, wherein said method comprises analyzing the bisulfite convertibility of at least one CpG position in the CD8 beta and CD8 alpha cell specific bisulfite convertibility gene region according to SEQ ID No. 1 and 2, wherein a bisulfite convertibility of at least one CpG position in said gene regions is indicative for a CD3+CD8+ and/or CD3+/−CD8+ cell. The analyses according to the invention can identify CD3+CD8+ and/or CD3+/−CD8+ cells on an epigenetic level and distinguish them from all other cells in complex samples, such as, for example, other blood cells. The present invention furthermore provides an improved method for quantifying CD3+CD8+ and/or CD3+/−CD8+ cells in complex samples, in particular based on a comparison of the CD8 beta and alpha gene bisulfite convertibility with a bisulfite convertibility of at least one marker selected from the group of CD3, CD4, FOXP3, NKT, NK, T helper cells and/or GAPDH. The method can be performed without a step of purifying and/or enriching cells, preferably in whole blood and/or non-trypsinized tissue.

Furthermore, the present invention relates to a kit for performing the above methods as well as respective uses thereof. It is one aim of this invention to provide a novel, more robust means to quantitatively detect and measure particular subsets of CD8+ cells of the blood within any solid organs or tissue or any body fluid of a mammal. Employing this method, the inventors provide novel, not previously known means for determining, quantifying and routinely measuring CD8 alpha/beta and CD8 alpha/alpha cells.

BACKGROUND OF THE INVENTION

CD8 (cluster of differentiation 8) is a transmembrane glycoprotein expressed on the surface of cytotoxic T-cells, but also of natural killer cells, cortical thymocytes and dendritic cells. CD8 forms a homo- or heterodimer comprised of either CD8 alpha and/or CD8 beta chains. CD8 interacts with class I MHC receptors during antigen-specific activation, functions as a co-receptor which associates with protein tyrosine kinase p56lck, and participates in T-cell receptor-mediated activation. According to current research, homodimers only exist as alpha/alpha chains and are expressed by $CD3+/^{-}CD8^{+}$ cells (cytotoxic T cells, NKT cells), whereas the heterodimer alpha/beta is expressed by $CD3^{+}CD8^{+}$ cells only. In humans, the CD8 alpha and beta molecules are encoded by CD8 alpha gene and CD8 beta gene.

T-lymphocytes are a major component of the mammalian immune system. Cytotoxic CD3+CD8+ T-cells are an important part of the cell-mediated immunity and hence mediating the cytotoxic immune defense. CD8+ cytotoxic T-cells lyse cells displaying epitopes of foreign antigens on their surface in order to kill infected, cancerous or damaged cells to prevent cancer, autoimmunity or infection. Natural killer cells, cortical thymocytes, and dendritic cells do not belong to cytotoxic T cells but express CD8 protein as well.

Even though almost all cells in an individual contain the exact same complement of DNA code, higher organisms must impose and maintain different patterns of gene expression in the various types of tissue. Most gene regulation is transitory, depending on the current state of the cell and changes in external stimuli. Persistent regulation, on the other hand, is a primary role of epigenetics-heritable regulatory patterns that do not alter the basic genetic coding of the DNA. DNA methylation is the archetypical form of epigenetic regulation; it serves as the stable memory for cells and performs a crucial role in maintaining the long-term identity of various cell types. Recently, other forms of epigenetic regulation were discovered. In addition to the "fifth base" 5-methylcytosine (mC), a sixth (5-hydroxymethylcytosine, hmC), seventh (5-formylcytosine, fC) and eighth (5-carboxycytosine, cC) can be found (Michael J. Booth et al. Quantitative Sequencing of 5-Methylcytosine and 5-Hydroxymethylcytosine at Single-Base Resolution Science 18 May 2012, Vol. 336 no. 6083 pp. 934-937).

The primary target of mentioned DNA modifications is the two-nucleotide sequence Cytosine-Guanine (a 'CpG site'); within this context cytosine (C) can undergo a simple chemical modification to become formylated, methylated, hydroxymethylated, or carboxylated. In the human genome, the CG sequence is much rarer than expected, except in certain relatively dense clusters called 'CpG islands'. CpG islands are frequently associated with gene promoters, and it has been estimated that more than half of the human genes have CpG islands (Antequera and Bird, Proc Natl Acad Sci USA 90: 11995-9, 1993).

Aberrant methylation of DNA is frequently associated with the transformation from healthy to cancerous cells. Among the observed effects are genome-wide hypomethylation, increased methylation of tumor suppressor genes, and hypomethylation of many oncogenes (reviewed, for example, by Jones and Laird, Nature Genetics 21:163-167, 1999; Esteller, Oncogene 21:5427-5440, 2002; and Laird, Nature Reviews/Cancer 3:253-266, 2003). Methylation profiles have been recognized to be tumor specific (i.e., changes in the methylation pattern of particular genes or even individual CpGs are diagnostic of particular tumor types), and there is now an extensive collection of diagnostic markers for bladder, breast, colon, esophagus, stomach, liver, lung, and prostate cancers (summarized, for example, by Laird, Nature Reviews/Cancer 3:253-266, 2003).

For one of the recently described modification of cytosine, 5-hydroxymethylation, the utility of oxidative bisulfite sequencing to map and quantify 5 hmC at CpG islands was shown (Michael J. Booth et al. Quantitative Sequencing of 5-Methylcytosine and 5-Hydroxymethylcytosine at Single-Base Resolution Science 18 May 2012, Vol. 336 no. 6083 pp. 934-937). High levels of 5 hmC were found in CpG islands associated with transcriptional regulators and in long interspersed nuclear elements. It is suggested that these regions might undergo epigenetic reprogramming in embryonic stem cells.

It is commonly thought that immune cell quantification is relatively easy and fully standardized, since the non-adherent, non-matrixed cells in peripheral blood can be marked with antibodies and flow-cytometrically quantified. Providing that cells are non-adherent, single cell suspensions, intact and cell-type specific surface antigens are available, flow cytometry is indeed a highly accurate cell quantification tool.

However, for many applications in research and medical routine, the named prerequisites for such precise measurements are not given:

1. Often, the material/samples measured are not derived from peripheral blood and thus the solubility and single cell suspension property is not met. This is, for example, true for all biopsy analyzes, such as performed in the pathological routine.

2. Even if the analyte is peripheral blood, the prerequisite of having intact cells is difficult to meet, since—in order to maintain their structural integrity ("intactness")—these cells must not be frozen or stored as EDTA-blood for more than 6 hours, before subfractions, such as granulocytes start disintegrating.

3. In contrast to the common perception, there are not highly specific (surface) antigens for all immune cell types and hence the identification of cell types is not as unambiguous as may be hoped. Since antigen expression is not a digital process, thresholds must be defined to decide, whether cells belong to the positive or negative fraction. For T cells, this problem is particular apparent:

Hence, for many applications the current methodological approaches for a quantitative determination of immune cells remain problematic, such as for routine testing in clinical applications, which usually requires some lag times, and hence robustness and stability of the analyte. As said, the flow cytometric methods used for measurement of cells in peripheral blood are not adequate for immune cells infiltrating other tissues, including solid tissues during tumor development or at/after inflammation. Hence, flow cytometric methods are not applied in these areas and the surrogate methods (mostly immune histochemistry) are at most semi-quantitative methods.

Hamerman et al. (in: Hamerman J A, Page S T, Pullen A M. Distinct methylation states of the CD8 beta gene in peripheral T cells and intraepithelial lymphocytes. J Immunol. 1997 Aug. 1; 159(3):1240-6) describe the CD8 co-receptor as expressed on both immature and mature T cells as either an alpha-beta heterodimer or an alpha alpha homodimer. Thymocytes and peripheral T cells express CD8 alpha-beta, whereas TCR alpha-beta+ intraepithelial lymphocytes (IEL) express CD8 alpha alpha or CD8 alpha-beta, and the majority of TCR gamma-delta+ IEL bear CD8 alpha alpha. The presence of CD8 beta enhances the signaling and adhesion properties of the CD8 alpha-beta coreceptor and is necessary for efficient T cell development in the thymus, but is not required for the extrathymic maturation of CD8 alpha alpha+ IEL. To address whether CD8 alpha alpha+ IEL express CD8 beta during their development, Hamerman et al. examined the methylation state of cytosines in the CD8 beta gene 5' regulatory region to identify those for which the methylation state inversely correlates with expression of the CD8 beta protein. They identified four such cytosines that were demethylated in CD8 beta-expressing thymocytes and T cells. Interestingly, these cytosines were also demethylated in CD4+ lymph node T cells that had transiently expressed CD8 beta during their development. The methylation state of these cytosines was examined in DNA purified from TCR alpha-beta+ CD8 alpha alpha+ and TCR alpha-beta+ CD8 alpha-beta+ IEL, as well as from TCR gamma-delta+ CD8 alpha alpha+ and CD3− CD8 alpha alpha+ IEL. The methylation pattern for TCR alpha-beta+ CD8 alpha alpha+ IEL DNA was distinct from that seen for DNA from CD4+ lymph node cells, suggesting that TCR alpha-beta+ CD8 alpha alpha+ IEL have not previously expressed CD8 beta. Analysis of DNA from CD3− CD8 alpha alpha+ IEL indicated that the unique methylation pattern of the CD8 beta gene in TCR alpha-beta+ CD8 alpha alpha+ IEL DNA was not due to transcription of the CD8 alpha gene or the influence of the gut microenvironment.

EP 1 213 360 describes a method of identifying a cell, tissue or nucleus, comprising collecting information on the methylation pattern of DNA isolated from the cell, tissue or nucleus and analyzing the resultant information.

WO 2008/132755 describes a test kit method for estimating CD4+/CD8+ T-cells based on anti-CD4+, anti-CD8+ monoclonal antibody detection carried out on microscopic glass slide. Additional staining visualizes T-cells to further enumeration under a microscope.

WO 02/083162 describes a method to treat, inhibit or prevent immune-driven rejection of grafted tissue or cells in a recipient host by administering a pharmaceutically effective amount of CD8+ T cell inhibitory agent.

EP 2058399 describes methods and reagents for vaccination which generate a CD8 T cell immune response.

EP 1753452 describes a method for altering the CD4/CD8 ratio and the mononuclear cellular infiltrate into a tumor whereby CD8 T cell level strongly decreases.

EP 1616016 describes gene therapy vectors having reduced immunogenicity based on CD8 alpha-chain finding use in extending the survival of transplant allografts and treating graft versus host disease in transplant recipients.

The above mentioned inventions require precise quantification on CD8 and it s subpopulations, which the present invention provides by a new methodology to effectively detect and quantify CD3+CD8+ and/or CD3+/−CD8+ cells, in particular for the first time detect and quantify CD8+ beta cells. Moreover the present invention enables flexible preclinical time framing which is not dependent on quick sample processing but rather allows long term sample storage and individual coordination between sample collecting and sample processing.

Furthermore, the publications of Melvin et al. (Hypomethylation in IFN-Gamma Gen correlates with expression of IFN-G, including CD8 cells, Eur J Immunol. 1995 February; 25(2):426-30), Landolfi M M et al. (CD2−CD4−CD8− lymph node T lymphocytes in MRL lpr/lpr mice are derived from a CD2+CD4+CD8+ thymic precursor J Immunol. 1993 Jul. 15; 151(2):1086-96), and Carbone A M et al. (Demethylation in CD8 suggests that CD4+ derives from CD8+ cells. Role of methylation pattern during cell development. Science. 1988 Nov. 25; 242(4882):1174-6) disclose methylation in connection with expression and differentiation.

WO 2008/132755 describes the identification of CD8 using immune histological methods.

While the measurement and determination of CD8+ cells is generally easy and is usually achieved through analyzing the expression of CD8 on the cellular surface, clinically, it remains challenging to specifically detect, identify, discriminate, and quantify actual CD3+CD8+ alpha/beta cells from whole CD8+ cells. Currently, clinical routine application is limited to the detection of CD8+ cells via detection of CD8 alpha and therefore lacks an established method to differentiate between CD3+CD8+ and CD3+/−CD8+ as well as to detect CD8 beta.

In view of the above, it is an object of the present invention to provide an improved and in particular robust method based on cytosine bisulfite convertibility analysis as a superior tool in order to more conveniently and reliably detect, identify, discriminate, and quantify CD3+/− subpopulations of CD8+ cells.

The present invention solves the above object by providing method for identifying subpopulations of cytotoxic T cells, comprising analyzing the bisulfite convertibility of at least one CpG position in a gene selected from the group of $CD8^+$ alpha and $CD8^+$ beta, wherein a bisulfite convertibility of at least one CpG position in the $CD8^+$ beta gene is indicative for a CD3+CD8+ cytotoxic T cell, and a bisulfite convertibility of the $CD8^+$ alpha gene is indicative for a CD3+/−CD8+ cytotoxic T cell.

Currently, no data describing CD8+ beta/beta cells exists. However, in a preferred embodiment thereof, the present invention for the first time will allow detection of such cells. Moreover, it is expected that the novel marker for CD8 beta will reveal new scientific insight into cell origin and cell state of CD8 beta chain expressing cells.

Currently, it is described in the literature that CD3+CD8+ NKT cells express the CD8 beta chain. However, the results of the present inventors indicate that for a portion of these cells there may exist a different epigenetic regulation that does not simply reflect or correspond to the currently known protein expression pattern.

As mentioned above, recently three new cytosine modifications were discovered. Therefore, it is expected that future scientific findings will correct epigenetic patterns of modification described in the past. These past patterns of cytosine modification encompass bisulfite convertible (non-methylated, non-modified) and non-convertible (methylated, modified) cytosine. Both termini need to be corrected, as described. According to the novel scientific findings (i) non-bisulfite convertible cytosine encompasses 5-methylcytosine (mC) and 5-hydroxymethylcytosine (hmC), and (ii) bisulfite convertible (i.e. the "bisulfite convertibility") cytosine encompasses 5-formylcytosine (fC), 5-carboxycytosine (cC), as well as non-modified cytosine.

Additionally, past inventions are based on (i) the ratio of bisulfite convertible cytosine to whole amount of chromatin (cell-type independent, 100% bisulfite convertible DNA locus) or (ii) on the ratio of bisulfite convertible cytosine (fC, cC, non-modified cytosine) to non-bisulfite convertible cytosine (hmC and mC). These ratios characterize cell type, cell differentiation, cell stage as well as pathological cell stages. Therefore, new techniques will result in novel, more specific ratios and might supplement current cell specific, cell state specific as well as pathological patterns of epigenetic modifications and therefore, define potential novel biomarkers. Novel ratios to be discovered as biomarkers can be defined as:

$$\text{Biomarker Ratio} = a/b$$

$a = \Sigma(\text{C and/or mC and/or hmC and/or fC and/or cC})$

$b = \Sigma(\text{C and/or mC and/or hmC and/or fC and/or cC})$,

whereby a and b differs from each other by one to four kinds of modifications. Discovery of novel DNA modifications will enlarge this enumeration.

For the purpose of definition for the present application, "epigenetic modifications" in the DNA sequence is referred to by the terminology of (i) bisulfite convertible cytosine (5-formylcytosine, (fC) and/or 5-carboxycytosine (cC)) and (ii) non-bisulfite convertible cytosine ((including 5-methylcytosine (mC), 5-hydroxymethylcytosine, (hmC)). As both kinds of methylation, mC and hmC, are not bisulfite convertible, it is not possible to distinguish between these two. Likewise, fC, cC as well as non-modified cytosine are bisulfite convertible and can also not be distinguished from each other as well. The term "methylated" DNA encompasses mC as well as hmC. The term "non-methylated" DNA encompasses fC, cC, and non-modified DNA. It is expected that novel variants of DNA modifications will be discovered in future. Each type of modification will be either bisulfite convertible or not. However, since the present method reliably distinguishes between the two groups, these novel modifications will also be usable as markers.

Furthermore, apart from the modifications of DNA, also histones undergo posttranslational modifications that alter their interaction with DNA and nuclear proteins. Modifications include methylation, acetylation, phosphorylation, ubiquitination, sumoylation, citrullination, and ADP-ribosylation. The core of the histones H2A, H2B, and H3 can also be modified. Histone modifications act in diverse biological processes such as gene regulation, DNA repair, chromosome condensation (mitosis) and spermatogenesis (meiosis). Also for these modifications a specific pattern of modification is specific for different cell types, cell stages, differentiation status and such a pattern can be analyzed for bisulfite convertibility or similar methods in order to identify certain cells and cell stages. The present invention also encompasses a use of these modifications.

The present invention is based on the surprising identification of a region of the CD8 gene by the inventors, namely the CD8 beta and alpha gene region, as specific epigenetic markers, allowing for the first time the identification of CD8 subpopulations of CD8 beta and alpha chain bearing cells as well as the clinical routine application of said analysis.

In the context of the present invention, the genomic region according to SEQ ID No. 1 is herein designated "CD8 beta chain specific bisulfite convertible region", which allows the identification of CD3+CD8+ cytotoxic T cells (alpha/beta CD8+ cells), and the genomic region according to SEQ ID No. 2 is herein designated "CD8 alpha chain specific bisulfite convertible region", which allows the identification of $CD3^{+/-}CD8^+$ cells (alpha/alpha CD8+ cells). Surprisingly, the discriminatory pattern of bisulfite convertible and non-convertible cytosine is exclusively limited to the genomic region according to SEQ ID No. 1 for CD8 beta bearing CD8+ cells as shown using the amplicons according to SEQ ID No. 5 and/or SEQ ID No. 6, and to the genomic region according to SEQ ID No. 2 for CD8 alpha bearing CD8+ cells as shown using the amplicon according to SEQ ID No. 7.

In a preferred embodiment of the method according to the present invention, both genes for $CD8^+$ alpha and $CD8^+$ beta are analyzed, preferably by analyzing amplicons derived from SEQ ID No. 1 and SEQ ID No. 2, and/or the CD8alpha specific non-methylated region derived from SEQ ID No. 3 and/or the CD8beta specific non-methylated region derived from SEQ ID No. 4.

In a preferred embodiment of the method according to the present invention for identifying a subpopulation of cytotoxic T cells (identification of CD3+CD8+ cells), said at least one CpG position is selected from a CpG position in an amplicon according to SEQ ID No. 2 and 3, and is preferably selected from positions 67, 92, 116, 123, 133, 161, 199, 231, 255, 267, and 291 in the amplicon No. 2004 according to SEQ ID No. 7 (CD8 alpha Assay), and positions 40 63 95 135 142 169 194 213 216 232, 245, 273, 339, 345, and 393 in the amplicon No. 2007 according to SEQ ID No. 5, and

positions 165, 196, 219, 267, 277, 307, 314, 341, and 410 in the amplicon No. 2008 according to SEQ ID No 6 (CD8 beta Assays).

The inventive concept is based on the specific bisulfite convertibility of the CD8 beta and CD8 alpha specific region in CD8 positive cells. Using a simple and precise quantitative PCR method, the inventors show that specific pattern of cytosine modification of the said gene regions represents a specific marker for CD3+CD8+ and CD3+/−CD8+ cell counts in blood or tissues. In one preferred embodiment, one highly discriminative region of the CD8 beta and CD8 alpha gene is designated by the nucleotide sequence according to SEQ ID No. 3, and SEQ ID No. 4, which displays differential bisulfite convertibility when alpha/beta and alpha/alpha CD8+ cells are compared with all other cells.

The inventors could demonstrate that in the CD8 beta bearing cells the CpG motifs are almost completely convertible by bisulfite (i.e. to more than 70%, preferably 80%, preferably, more than 90% and most preferred more than 95%), whereas the same motifs are completely methylated in all $CD8^-$ and alpha/alpha CD8+ cells. In the same context, the inventors could demonstrate that in the CD8 alpha bearing cells the CpG motifs are almost completely convertible by bisulfite as well (i.e. to more than 70%, preferably 80%, preferably, more than 90% and most preferred more than 95%), whereas the same motifs are completely methylated in all $CD8^-$ cells.

The differential methylation of the CpG motifs within the aforementioned regions correlates with expression of CD8 alpha and beta chains. Thus, determination of the bisulfite convertibility of the CD8 alpha and beta locus is a valuable tool to identify subpopulations of CD8+ cells, such as will be required/or at least of some value for identifying and quantifying said cells in autoimmune diseases, transplant rejections, cancer, allergy, primary and secondary immunodeficiencies, such as, for example, HIV infections and AIDS, Graft versus Host (GvH), hematologic malignancies, rheumatoid arthritis, multiple sclerosis, or a cytotoxic T cell related immune status in any envisionable diagnostic context. The assay allows measurement of CD8+ subpopulations without purification or any staining procedures. It even reports in solid tumors or other solid tissues the number of cells bisulfite convertible in said region, thus showing the total amount of tumor infiltrating CD8+ subpopulations.

The inventors found a bisulfite convertibility at the human CD8 beta and alpha locus to be restricted to CD3+CD8+ and CD3+/−CD8 cells, respectively, when tested against all major peripheral blood cell types. These data indicated that epigenetic modifications in the CD8 beta and alpha locus serve as valuable markers for the identification CD8+ subpopulations, regardless of the expression of both, CD8 beta and alpha chain.

Another preferred aspect of the method according to the present invention then further comprising a quantification of the relative amount of CD3+CD8+ and/or CD3+/−CD8+ cells based on comparing the relative amount(s) of bisulfite convertible DNA in regions specific for CD8 alpha and/or beta with the relative amount(s) of non-bisulfite convertible DNA of cell-specific regions. Said quantification thus is achieved based on the ratio of the bisulfite convertible DNA to non-convertible DNA in the genetic regions of CD8 beta and alpha as described and analyzed herein. Most preferred is a quantification of the relative amount of CD3+CD8+ and/or CD3+/−CD8+ cells is based on an (preferably parallel or simultaneous) analysis of the relative amount of bisulfite convertible DNA of cell-specific regions for CD8 alpha and/or beta, and of the relative amount of bisulfite convertible DNA of cell-unspecific genes (preferably designated "control genes" or "control regions", such as, for example, the gene for GAPDH). The analysis preferably further comprises an analysis of the bisulfite convertibility of at least one CpG position in a gene selected from cell-specific genes of CD3 T cells, CD4 T cells, regulatory T cells, monocytes, granulocytes, B cells, GAPDH, Th1, Th2, Th9, Th17, Th22, Tfh, NKT, and NK. In some embodiments, ratios of markers and respective numbers and/or amounts of cells can be determined and established based on, at least in part, the present analysis, for example of CD8+ beta to CD8+ alpha, overall CD8+ (alpha+ beta) to overall CD3+, CD8+ beta to CD3+, CD8+ alpha to CD3+, and/or CD3+CD8+ to CD3+CD4+, and/or CD8+ beta or CD8+ alpha to Treg or overall CD8+ to Treg cells and/or markers, in a sample to be analyzed.

In a further preferred embodiment of the method according to the present invention, said analysis of bisulfite convertibility comprises amplification with at least one primer of suitable primer pairs that can be suitably designed based on SEQ ID No. 1 or SEQ ID 2, preferably oligomers according to any of SEQ ID No. 8 to 13.

In contrast to FACS and mRNA measurements, using the methods according to the present invention, the measurement(s) and analyses can be done independent of purification, storage—and to quite some extent—also to tissue quality.

Preferably, the amplification involves a polymerase enzyme, a PCR or chemical amplification reaction, or other amplification methods as known to the person of skill as described below, e.g. in the context of MSP, HeavyMethyl, Scorpion, MS-SNUPE, MethylLight, bisulfite sequencing, methyl specific restriction assays and/or digital PCR (see, for example Kristensen and Hansen PCR-Based Methods for Detecting Single-Locus DNA Methylation Biomarkers in Cancer Diagnostics, Prognostics, and Response to Treatment Clinical Chemistry 55:8 1471-1483 (2009)).

With the amplification, an amplicon of the CD8 beta and alpha gene is produced that is a particularly preferred "tool" for performing the method(s) according to the present invention. Consequently, oligomers according to any of SEQ ID No. 8 to 13 or an amplicon as amplified by a primer pair based on SEQ ID No. 1 or 2 as mentioned above constitute preferred embodiments of the present invention.

The person of skill will furthermore be able to select specific subsets of CpG positions in order to minimize the amount of sites to be analyzed, for example at least one of CpG position 40, 63, 95, 135, 142, 169, 194, 213, 216, 232, 245, 273, 339, 345, 393, 165, 196, 219, 267, 277, 307, 314, 341, and 410 of the $CD8^+$ beta specific bisulfite convertible region (SEQ ID No. 1 or 4), or all sites as present on the $CD8^+$ beta specific bisulfite convertible region according to SEQ ID No 1 or 4. The positions are numerically counted from the 5'-end of an amplicon (e.g. positions 40, 63, 95, 135, 142, 169, 194, 213, 216, 232, 245, 273, 339, 345, and 393 in the amplicon No. 2007 according to SEQ ID No. 5, and positions 165, 196, 219, 267, 277, 307, 314, 341, and 410 in the amplicon No. 2008 according to SEQ ID No. 6) as generated and analyzed. Preferred are combinations of 3, 4, 5, 6, 7, 8, 9, or 10 positions, the analysis of which produces sufficient data and/or information in order to be informative in the context of the present invention, such as, for example, positions 142, 169, 194, 213, 216, 232, 245, 273, in the amplicon No. 2007 according to SEQ ID No. 5.

The person of skill will furthermore be able to select specific subsets of CpG positions in order to minimize the amount of sites to be analyzed, for example at least one of

CpG position 67, 92, 116, 123, 133, 161, 199, 231, 255, 267, and 291 of the CD8+ alpha specific bisulfite convertible region (SEQ ID No. 2 or 3), or all sites as present on the CD8+ alpha specific bisulfite convertible region according to SEQ ID No 2 or 3. The positions are numerically counted from the 5'-end of an amplicon (e.g. positions 67, 92, 116, 123, 133, 161, 199, 231, 255, 267, and 291 in the amplicon No. 2004 according to SEQ ID No. 7) as generated and analyzed. Preferred are combinations of 3, 4, 5, 6, 7, 8, 9, or 10 positions, the analysis of which produces sufficient data and/or information in order to be informative in the context of the present invention, such as, for example, positions 116, 123, 133, 161, 199, 231, 255, 267 in the amplicon No. 2004 according to SEQ ID No. 7.

In order to analyze the bisulfite convertibility of CpG positions, any known method to analyze DNA modification can be used. In a preferred embodiment of the method according to the present invention, the analysis of the DNA modification comprises a method selected from single molecule real-time technology (SMRT), DNA-modification-dependent polymerase kinetics, DNA sequencing through nanopores, strand sequencing, exonuclease sequencing, DNA-modification-dependent DNA hybridization, methylation specific enzymatic digests, bisulphite sequencing, analysis selected from promoter methylation, CpG island methylation, MSP, HeavyMethyl, MethyLight, Ms-SNuPE or other methods relying on a detection of amplified DNA. These methods are well known to the person of skill, and can be found in the respective literature.

In a preferred embodiment of the method according to the present invention, said method is suitable for routine application, for example on a DNA-chip. Based on the above information and the respective literature, the person of skill will be able to adjust the method as above to such settings.

In yet another preferred embodiment of the methods according to the present invention, said method is performed without a step of purifying and/or enriching said cells to be identified, preferably using whole blood and/or non-trypsinized tissue.

In another preferred embodiment of the method according to the present invention, the identification comprises a distinction of said CD3+CD8+ and CD3+/−CD8+ cells from all major peripheral blood cell types and/or non-blood cells, preferably, but not limited to, from CD19+ B lymphocytes, CD3+CD8+ T-Cells, CD15+ granulocytes, CD14+ monocytes, CD56+ Natural Killer Cells and CD3+CD56+ Natural Killer T-Cells, and CD3+CD4+ T helper cells, and other cell types derived from other organs than blood.

In yet another preferred embodiment of the method according to the present invention, the sample is selected from a mammalian body fluid, including human blood samples, or a tissue, organ or a sample of leukocytes or a purified or separated fraction of such tissue, organ or leukocytes or a cell type sample. Preferably, said mammal is a mouse, rat, monkey or human. The samples can be suitably pooled, if required.

Another preferred aspect of the method according to the present invention then further comprises the step of concluding on the immune status of said mammal based on said CD8+ subpopulations. The CD8+ subpopulations can be quantified and be used as a benchmark to relatively quantify further detailed subpopulations (as but not limited to CD4, Th1, Th2, Th9, Th17, Th22, Treg, Tth), or it can be used as a predictive and/or screening and/or diagnostic and/or prognostic and/or adverse events detecting factor, or it can be used to finally detect this population to determine the overall immune activity status.

Another preferred aspect of the method according to the present invention is directed at the use of cytosine modification analysis of cell specific genes for CD3+, CD4+, regulatory T cells, Th1, Th2, Th9, Th17, Th22, Tfh, NKT, NK, monocytes, granulocytes and/or B cells for the detection and quality assurance and control of alpha/beta and/or alpha/alpha CD8+ cells.

In yet another preferred embodiment of the methods according to the present invention, the mammal suffers from or is likely to suffer from autoimmune diseases, transplant rejections, infection diseases, cancer, and/or allergy as but not limited to *Trypanosoma cruzi*-infection, Malaria and HIV infection; Hematologic Malignancies as but not limited to chronic Myelogenous Leukemia, Multiple Myeloma, Non Hodgkin's Lymphoma, Hodgkin's Disease, chronic Lymphocytic Leukemia, Graft versus Host and Host versus Graft Disease, Mycosis fungoides, Extranodal T cell lymphoma, Cutaneous T cell lymphomas, Anaplastic large cell lymphoma, Angioimmunoblastic T cell lymphoma and other T-cell, B-cell and NK cell neoplasms, T cell deficiencies such as but not limited to lymphocytopenia, severe combined immunodeficiency (SCID), Omenn syndrome, Cartilage-hair hypoplasia, acquired immune deficiency syndrome (AIDS), and hereditary conditions such as DiGeorge syndrome (DGS), chromosomal breakage syndromes (CBSs), multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, dermatomyositis, primary biliary cirrhosis, primary sclerosing cholangitis, ulcerative colitis, Crohn's disease, psoriasis, vitiligo, bullous pemphigoid, alopecia areata, idiopathic dilated cardiomyopathy, type 1 diabetes mellitus, Graves' disease, Hashimoto's thyroiditis, myasthenia gravis, IgA nephropathy, membranous nephropathy, and pernicious anemia; and B-cell and T-cell combined disorders such as but not limited to ataxia telangiectasia (AT) and Wiskott-Aldrich syndrome (WAS); and carcinomas such as but not limited to breast cancer, colorectal cancer, gastric cancer, pancreatic cancer, hepatocellular carcinoma, cholangiocarcinoma, melanoma, and head and neck cancer.

Another preferred aspect of the method according to the present invention then relates to a method as above, further comprising measuring and/or monitoring the amount of CD3+ CD8+ and/or CD3+/−CD8+ cells in response to chemical and/or biological substances that are provided to said mammal, i.e. in response to a treatment of said patient. Said method comprises the steps as above, and comparing said relative amount of said cells as identified to a sample taken earlier or in parallel from the same mammal, and/or to a control sample. Based on the results as provided by the method(s) of the invention, the attending physician will be able to conclude on the immune status of the patient, and adjust a treatment of the underlying disease accordingly.

Preferably, said method is performed without a step of purifying and/or enriching cells, preferably in whole blood and/or non-trypsinized tissue, or any other biological sample potentially containing said subpopulations of CD8+ cells as e.g. a sample for cell transfer into a patient.

Another preferred aspect of the method according to the present invention then relates to a method as above, further comprising formulating said subpopulation of cells as identified for transplantation into a patient. Pharmaceutical preparations for these purposes and methods for their production are performed according to methods known in the art of transplantation medicine.

Another preferred aspect of the method according to the present invention relates to an oligomer according to any of SEQ ID No. 8 to 13, an oligomer designed based on SEQ ID

No. 1 or 2, the CD8 alpha and/or beta gene specific non-methylated region according to SEQ ID No. 3 or 4 or an amplicon selected from any of SEQ ID No. 3 to 7.

Yet another preferred aspect of the present invention then relates to a kit for identifying and/or monitoring said CD8 subpopulations (CD3+CD8+ cells and/or CD3+/−CD8+ cells) in a mammal based on the analysis of the bisulfite convertibility of at least one CpG position in the CD8 beta and CD8 alpha cell specific bisulfite convertible gene regions according to SEQ ID No. 1 and 2, respectively, and/or at least one amplicon selected from any of SEQ ID No. 3 to 7, respectively, comprising materials for performing a method according the present invention as described herein. Preferably, said kit comprises a) a bisulfite reagent, and b) materials for the bisulfite convertibility analysis of at least one CpG position selected from the positions 67, 92, 116, 123, 133, 161, 199, 231, 255, 267, and 291 in the amplicon No. 2004 according to SEQ ID No. 7, and positions 40, 63, 95, 135, 142, 169, 194, 213, 216, 232, 245, 273, 339, 345, and 393 in the amplicon No. 2007 according to SEQ ID No. 5, and positions 165, 196, 219, 267, 277, 307, 314, 341, and 410 in the amplicon No. 2008 according to SEQ ID No. 6. Further preferred, the positions consist of all positions in the $CD8^+$ cell specific non-methylated region according to SEQ ID No. 1 and 2, respectively, and/or said amplicons according to any of SEQ ID Nos. 3 to 7, or positions 142, 169, 194, 213, 216, 232, 245, 273, in the amplicon No. 2007 according to SEQ ID No. 5 and/or positions 116, 123, 133, 161, 199, 231, 255, 267 in the amplicon No. 2004 according to SEQ ID No. 7.

The present invention also encompasses the use of oligomers or amplicon or a kit according to the present invention for identifying and/or for monitoring $CD3^+CD8^+$ and/or $CD3^{+/-}CD8^+$ cells in a mammal as described herein.

In summary, using the CD8 beta and alpha marker, the inventors very specifically identified, quantified and particularly differentiated both CD8 positive cells as such and its subpopulations, and in their relation to other cell types in a sample, for example to overall T-lymphocytes using the epigenetic markers for CD3, or their association to the CD4 T helper cells using the marker CD4. By such means for example CD4 positive T-lymphocytes could then be further distinguished from CD8 lymphocytes. This was not possible before the invention, since the protein expression of the marker CD8 beta and alpha cannot be used to reliable identify and quantify CD8 positive alpha/beta and alpha/alpha cells, nor was it possible from a (fresh, embedded or frozen) whole blood or tissue sample without specific means of conservation to provide a routine technology for the quantification of these cell types. Additionally, up to now no marker for CD8+ alpha/beta cells was discovered to identify and quantify said cells.

The invention will now be further described based on the following examples and with reference to the accompanying figures and the sequence listing, without being limited thereto. For the purposes of the present invention, all references as cited herein are incorporated by reference in their entireties. In the Figures and Sequences,

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** shows the analysis of CpG sites on amplicons No. 1482, No. 1483, No. 1484, No. 2006, No. 2007 (SEQ ID No. 3), No. 2008, No. 2009, No. 2010, No. 2011, and No. 2012, respectively, within the CD8 beta gene. The numbers on the left indicate the respective CpG position on the respective amplicon. The abbreviations at the bottom indicate B cells (CD3− CD8−)(BLC), cytotoxic T lymphocytes (CD3+ CD8+)(CTL), CD3−CD8− granulocytes (GRC) and CD3−CD8− monocytes (MOC), NK cells (CD3−CD8+)(NKC), NKT cells (CD3+CD8+)(NKT11), CD3+CD8− NKT cells (NKT14), and T helper cells (CD3+CD8−)(THC), respectively.

FIG. **2** shows the analysis of CpG sites on amplicons No. 1474, No. 1475, No. 1476, No. 1477, No. 1478 (SEQ ID No. 3), No. 1479, No. 1480, No. 1481, No. 2002, No. 2003, No. 2004, and No. 2005, respectively, within the CD8 alpha gene. The numbers on the left indicate the respective CpG position on the respective amplicon. The abbreviations at the bottom indicate B cells (CD3−CD8−)(BLC), cytotoxic T lymphocytes (CD3+CD8+)(CTL), CD3−CD8− granulocytes (GRC) and CD3−CD8− monocytes (MOC), NK cells (CD3− CD8+)(NKC), NKT cells (CD3+CD8+)(NKT11), CD3+CD8− NKT cells (NKT14), and T helper cells (CD3+ CD8−)(THC), respectively.

FIG. **3** shows the position of the specific bisulfite convertible regions within the CD8 beta gene according to the present invention, and the alignments of amplicons as analyzed (gray squares) against this region.

FIG. **4** shows the position of the specific bisulfite convertible regions within the CD8 alpha gene according to the present invention, and the alignments of amplicons as analyzed (gray squares) against this region.

FIG. **5** shows the comparison of qPCR and FCM measurements. (A) Ratio of $CD8^+$ to $CD3^+$ T-cells in (%) as determined by FCM (x-axis) and epigenetic qPCR measurement (y-axis) in peripheral blood of healthy controls (black circles) and HIV^+ patients (grey squares; white triangles). (B) Bland-Altman-diagrams for method agreement of $CD8^+$ to $CD3^+$ T-cells. Plotted is the mean of the determined ratios by both methods (x-axis) and the corresponding percentaged differences (FCM-qPCR). The solid line represents the estimated mean difference, dotted lines the estimated upper and lower limits of agreement.

SEQ ID No. 1 shows the CD8 beta chain specific bisulfite convertible region according to the present invention.

SEQ ID No. 2 shows the CD8 alpha chain specific bisulfite convertible region according to the present invention.

SEQ ID No. 3 shows the sequence of the CD8A specific non-methylated region (alpha); the sequence contains discriminatory amplicon 2004 (AMP2004), and is confined at the 5' and 3' end by the non-discriminatory AMP 2003 and AMP2005, respectively.

SEQ ID No. 4 shows the sequence of the CD8B specific non-methylated region; the sequence contains discriminatory overlapping amplicons AMP2007 and AMP2008. The sequence is confined at the 3' end by the non-discriminatory amplicons AMP2011 and AMP1479 (near the CD8alpha gene).

SEQ ID No. 5 and SEQ ID No. 6 show the sequences of amplicons Amp 2007 and Amp 2008 for CD8 beta (overlapping), respectively.

SEQ ID No. 7 shows the sequence of amplicon Amp 2004 for CD8 alpha.

SEQ ID No. 8 to SEQ ID No. 13 show the sequences of specific oligomers according to the present invention.

SEQ ID No. 14 to SEQ ID No. 25 show the sequences of specific oligomers according to the present invention; SEQ ID No. 14 shows the forward Primer (nmF1.3) for AMP 2007; SEQ ID No. 15 shows the reverse primer (nmR1.5) for AMP 2007; SEQ ID No. 16 shows the forward primer (mF1.3) for AMP 2007; SEQ ID No. 17 shows the reverse primer (mR1.9) for AMP 2007; SEQ ID No. 18 shows the

probe (nmP1.2), and SEQ ID No. 19 shows the probe (mP1.2); SEQ ID No. 20 shows the genomic sequence/position forward primer (nmF1.3) for AMP 2007; SEQ ID No. 21 shows the genomic sequence/position of reverse primer (nmR1.5) for AMP 2007; SEQ ID No. 22 shows the genomic sequence/position of forward primer (mF1.3) for AMP 2007; SEQ ID No. 23 shows the genomic sequence/position of reverse primer (mR1.9) for AMP 2007; SEQ ID No. 24 shows the genomic sequence/position of probe (nmP1.2) for AMP 2007, and SEQ ID No. 25 shows the genomic sequence/position of probe (mP1.2) for AMP 2007.

EXAMPLES

Example 1

The inventors have purified various blood subsets by FACS sorting including B cells (CD3− CD8−)(BLC), cytotoxic T lymphocytes (CD3+CD8+)(CTL), CD3−CD8− granulocytes (GRC) and CD3−CD8− monocytes (MOC), NK cells (CD3−CD8+)(NKC), NKT cells (CD3+CD8+) (NKT11), CD3+CD8− NKT cells (NKT14), and T helper cells (CD3+CD8−) (THC). DNA from the purified cells was bisulfite-treated and analyzed at various CpG dinucleotide motifs within the CD8 alpha and the CD8 beta gene. The inventors then compared the bisulfite convertibility (T for cytosine that was not-methylated in the original sequence versus finding C as for Cytosine that was methylated in the original (genomic) sequence).

The CD8 beta data (FIG. **1**) showed various CpG positions in the Amp 2007 of CD8 beta gene (see SEQ ID No. 1) that were non-methylated in CD3+CD8+ cytotoxic T-cells and partially non-methylated in CD3+CD8+ NKT cells while methylated in all other analyzed blood cell types. The differentially cytosine modified gene region Amp 2007 for CD8 beta is shown in SEQ ID No. 5.

Currently, it is described in the literature that CD3+CD8+ NKT cells express the CD8 beta chain. However, the results of the present inventors indicate that for a portion of these cells there may exist a different epigenetic regulation that does not simply reflect or correspond to the currently known protein expression pattern. This was also shown earlier for Treg cells and Th17 cells (see EP1826279 and PCT/EP2012/070676, both herewith incorporated by reference). Moreover, it is expected that the novel marker for CD8 beta will reveal new scientific insight into cell origin and cell state of CD8 beta chain expressing cells.

The CD8 alpha data (FIG. **2**) showed various CpG positions in the Amp 2004 of the CD8 alpha gene (see SEQ ID No. 2) that were non-methylated in CD3+CD8+ cytotoxic T-cells and in CD3+CD8+ NKT cells while methylated in all other analyzed blood cell types. The differentially cytosine modified gene region Amp 2004 for CD8 alpha is shown in SEQ ID No. 7. Similar to the bisulfite conversion pattern of CD8 beta, also for the CD8 alpha gene there was a partial methylation found for cells that in the literature are described as CD8 alpha protein expressing cells (NK cells). FACS sorting via protein expression does not reflect actual epigenetic regulation status. Future scientific studies on the epigenetic pattern in the CD8 alpha gene using the present epigenetic CD8 alpha marker will further deepen the understanding of e.g. origin and state of said cells.

Example 2: Assessment of $CD8^+$ CD3+ T-Cells in Human Peripheral Blood

Novel epigenetic assays were compared with flow cytometry assays for the detection of CD8 and CD3 cells and ratios thereof. As both techniques determine the same biological variable, they should be essentially concordant.

Human peripheral blood was obtained from healthy volunteers. DNA from venous blood was purified using DNeasy Blood&Tissue Kit (Qiagen) according to manufacturer instructions. Additionally, capillary blood was spotted on FTA® Cards (Whatman) and dried at room temperature overnight. DNA was extracted from 6×6 mm spots using QIAamp DNA Kit (Qiagen). Following, DNA was bisulfite converted: Up to 1.5 μg genomic DNA were converted applying Epitect (Fast) Bisulfite Kits (Qiagen) according to manufacturer's protocol. Whole blood DNA was purified using a Microcon®-30 Centrifugal Filter (Millipore). qPCR: Highly cell-type specific methylation-dependent qPCRs for quantification of $CD3^+$ and $CD8^+$ T-cells were developed and performed as follows: One set of oligonucleotides (i.e., forward/reverse primer and hydrolysis probe) specific for TpG- or CpG-variant was used. Reactions were carried out in triplicates in 10 μl total volume using 2×Probe Mastermix (Roche), 15 pmol of each primer, 1.25-2.5 pmol probe, 25 ng λ-DNA (NEB) and up to 82 ng template DNA or plasmid at 1×95° C. 10 min, and 50 cycles 95° C. 15 sec and 61° C. 60 sec. For CD8B TpG, $MgCl_2$ was added to a final concentration of 4.7 mM. Amplification crossing points were determined using LightCycler480 software (Roche) deploying the second-derivative maximum method. Percental target cells were calculated as previously described (Sehouli, J. et al. 2011. Epigenetic quantification of tumor-infiltrating T-lymphocytes. *Epigenetics* 6:236-246). For blood samples, normalization of qPCR values (x_N) was carried out as follows: $x_N = qPCR_x/qPCR_{Cal} * FCM_{Cal}$ using a calibrator (Cal) with a determined FCM value (FCM_{Cal}). Plasmids: Synthesized target regions for real-time qPCR assays were inserted into plasmid pUC57 or pJet1.2 (Genscript Inc.). Linearized plasmids were diluted in 10 ng/μl of λ-phage DNA (NEB) to obtain qPCR standards of 31250, 6250, 1250, 250, 50, and 30 copies per reaction.

Oligonucleotides: qPCR: The sequences of amplification primers are as follows:

(SEQ ID No. 14)
Forward Primer (nmF1.3) AMP 2007:
GGT TAA GAA ATT AAT AGG AAA AAG AAT

(SEQ ID No. 15)
Reverse primer (nmR1.5) AMP 2007:
CTT CCC CAC CAC AAT ACA ACA

(SEQ ID No. 16)
Forward primer (mF1.3) AMP 2007:
GGT TAA GAA ATT AAT AGG AAA AAG AAC

(SEQ ID No. 17)
Reverse primer (mR1.9) AMP 2007:
CCC CAT ATT ACT TCC CCG

The sequences of probes are as follows:

Probe (nmP1.2):
(SEQ ID No. 18)
TGT TTG TGA GGT ATT TAG TTG ATG GGA GTT TTG

Probe (mP1.2):
(SEQ ID No. 19)
CGT TTG TGA GGT ATT TAG TCG ACG GGA G

Genomic positions of amplification primers and probes are as follows:

Genomic forward Primer (nmF1.3) AMP 2007
(SEQ ID No. 20)
GGTTAAGAAACCAACAGGAAAAAGAAC

-continued

(SEQ ID No. 21)
Reverse primer (nmR1.5) AMP 2007:
CGTTGTATTGTGGCGGGGAAG

(SEQ ID No. 22)
Forward primer (mF1.3) AMP 2007:
GGTTAAGAAACCAACAGGAAAAAGAAC

(SEQ ID No. 23)
Reverse primer (mR1.9) AMP 2007:
CGGGGAAGCAACATGGGG

(SEQ ID No. 24)
Probe (nmP1.2) AMP 2007:
CGCCTGTGAGGCACTCAGCCGACGGGAGCTTTG

(SEQ ID No. 25)
Probe (mP1.2) AMP 2007:
CGCCTGTGAGGCACTCAGCCGACGGGAG

CD3- and GAPDH-qPCR positions of amplification primers and probes were described previously (Sehouli, J. et al. 2011. Epigenetic quantification of tumor-infiltrating T-lymphocytes. *Epigenetics* 6:236-246).

Flow cytometry: Cell sorting: Peripheral blood samples were fractionated in a MACS/FACS sorting protocol (Baron, U., Floess, S., Wieczorek, G., Baumann, K., Grützkau, A., Dong, J., Thiel, A., Boeld, T. J., Hoffmann, P., Edinger, M., et al. 2007. DNA demethylation in the human FOXP3 locus discriminates regulatory T cells from activated FOXP3(+) conventional T cells. *Eur J Immunol* 37:2378-2389.) for granulocytes ($CD15^+$), monocytes ($CD3^-$/$CD14^+$), NK cells ($CD56^+$/$CD16^+$), B cells ($CD19^+$), $CD8^+$ T-cells ($CD3^+$/$CD8^+$/$CD4^-$). Cell counting: 50 µl peripheral blood was stained in TruCount™ tubes (Becton-Dickinson) with anti-CD3 FITC, anti-CD4 PerCP and anti-CD8 APC. After staining and erythrocyte lysis, cells were analyzed on FACS-LSRII (Becton Dickinson). Absolute $CD3^+$ and $CD3^+$ $CD8^+$ T-cell counts per microliter of peripheral blood were calculated by the ratio between analyzed cells and fluorescent TruCount™ beads according to the manufacturer's instructions. Anti-CD45 PE staining was performed for assessment of relative cell counts.

Statistical analysis: For Bland-Altman plots, errors were given in percent (FCM-qPCR). Two-sided t-tests were performed to test if mean differences (bias) were significantly different from zero. Linear regression was performed to obtain slope and intercept. Shapiro-Wilk tests and Q-Q-Plots were used to assess normality assumptions of regression residuals. Residuals were visually inspected with respect to homogenous scattering. P-values <0.05 were considered significant. In ROC analysis optimal cutoff value and accuracy was determined as value minimizing the Euclidean distance to the coordinate point with optimal sensitivity and specificity. All p-values correspond to two-sided tests. Statistics software SPSS 21.0 (IBM) and R 2.14 were employed.

T-cell counts in peripheral blood. Randomly selected and blinded peripheral blood samples from 39 healthy and 86 HIV^+ donors were tested with epigenetic assays for CD3 and CD8B and compared with the according Flow-Cytometry (FCM)-based T-cell counting procedures. Healthy and HIV^+ subjects had a median age of 55 (range: 19-67) and 46 (range: 23-75) years, respectively. 87.2% of HIV^+ subjects were treated with anti-retroviral therapy and 17.4% had opportunistic infections.

Method agreement for CD8/CD3 ratio. The median CD8/CD3 ratio in healthy subjects was 21.0% in qPCR tests (FCM: 27.6%) ranging from 9.1%-34.7% (FCM: 15.1%-52.6%) while HIV^+ patients exhibited a median of 41.5% (FCM: 64.6%) ranging from 25.1%-60.9% (FCM: 34.1%-94.0%, FIG. **5**A). Pearson correlation between qPCR and FCM data was at 0.94 ($p<0.001$). The estimated mean difference in the Bland-Altman percent-difference diagram indicated a 34.1% smaller qPCR measurement compared to FCM (LoA: 66.6% and 1.6% (FIG. **5**B)). The inventors also tested agreement of epigenetic qPCRs for CD8/CD3 ratio between venous blood and dried capillary blood from six healthy donors (see Table A).

When employing these assays on whole blood, good method agreement between cell ratios obtained by qPCR and FCM was observed. Also, concordance was observed for clinically used FCM- and experimentally determined qPCR-cutoffs. qPCRs were also performed from dried blood spots and showed data equivalent to those from venous blood.

TABLE A

Evaluation of qPCR performance from dried blood spots compared to fresh blood according to Bland-Altman method.

	CD8/CD3 [%]	
	Venous blood	DBS
Donor 1	15.4	13.9
Donor 2	25.1	23.7
Donor 3	28.4	28.1
Donor 4	22.5	20.5
Donor 5	19.8	24.3
Donor 6	21.6	22.3
Mean	22.1	22.1
MD		0.00
upper LoA		4.8
lower LoA		−4.8

MD—mean difference, LoA—limits of agreement.

SEQUENCE LISTING

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<211> LENGTH: 46586
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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ggatacattt ggttccacaa gggggacact ttggggttca caaggatggg ggccacagct 120

-continued

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The invention claimed is:

1. A method for identifying $CD3^+CD8^+$ cytotoxic T cells in a sample derived from a human, wherein said method comprises:

i) providing the sample derived from the human comprising immune cells;

ii) determining the methylation status of at least one CpG position in genomic regions for $CD8^+$ beta consisting of the sequences of SEQ ID NO: 5 and 6, wherein said determining the methylation status comprises the steps of:

a) isolating genomic DNA from said sample,

b) treating the isolated genomic DNA with bisulfite,

c) amplifying a first genomic region in the bisulfite treated genomic DNA with a first primer pair of SEQ ID NOs: 8 and 9 to produce a first amplicon, wherein the first genomic region in the bisulfite treated genomic DNA corresponds to the genomic region consisting of SEQ ID NO: 5, and amplifying a second genomic region in the bisulfite treated genomic DNA with a second primer pair of SEQ ID NOs: 10 and 11 to produce a second amplicon, wherein the second genomic region in the bisulfite treated genomic DNA corresponds to the genomic region consisting of SEQ ID NO: 6,

d) performing a nucleic acid based assay on said first amplicon to determine the methylation status of the CpG positions 40, 63, 95, 135, 142, 169, 194, 213, 216, 232, 245, 273, 339, 345, and 393 in the first genomic region consisting of the sequence of SEQ ID NO: 5 and performing a nucleic acid based assay on said second amplicon to determine the methylation status of the CpG positions 165, 196, 219, 267, 277, 307, 314, 341, and 410 in the second genomic region consisting of the sequence of SEQ ID NO: 6; and

iii) identifying the immune cells as $CD3^+CD8^+$ cytotoxic T cells when the CpG positions in the first genomic region and the second genomic region are less than 20% methylated.

2. The method according to claim **1**, further comprising quantifying the relative amount of said $CD3^+CD8^+$ cytotoxic T cells, said quantifying comprising detecting the methylation status of a control gene and comparing said methylation status of the control gene with the methylation status of said CpG positions in SEQ ID NOs: 5 and 6.

3. The method according to claim **1**, wherein said nucleic acid based assay is performed on a DNA-chip.

4. The method according to claim **1**, wherein said $CD3^+CD8^+$ cytotoxic T cells as identified are further distinguished from cell types selected from the group consisting of $CD19^+$ B lymphocytes, $CD15^+$ granulocytes, $CD14^+$ monocytes, $CD56^+$ natural killer Cells, $CD3^+CD56^+$ natural killer T-Cells, and $CD3^+CD4^+$ T helper cells by comparing the methylation status of the CpG positions in SEQ ID NOs: 5 and 6.

5. The method according to claim **1**, wherein said sample is selected from a body fluid, tissue, organ or a blood lymphocyte or a fraction thereof.

6. The method according to claim **1**, wherein said method is performed without a step of purifying and/or enriching the immune cells in the sample derived from the human.

7. The method according to claim **1**, further comprising formulating said $CD3^+CD8^+$ cytotoxic T cells as identified for transplantation into a patient.

8. A method for monitoring the level of $CD3^+CD8^+$ cytotoxic T cells in a human, comprising performing the method according to claim **2**, and comparing said relative amount of the $CD3^+CD8^+$ cytotoxic T cells to a sample taken earner or in parallel from the same human and/or to a control sample.

9. The method according to claim **8**, further comprising treating said mammal with a chemical and/or biological substance, and measuring and/or monitoring the amount of said $CD3^+CD8^+$ cytotoxic T cells in response to said chemical and/or biological substance.

10. The method according to claim **1**, wherein said human suffers from or is likely to suffer from an autoimmune disease, transplant rejection, infectious disease, cancer, and/or allergy.

11. A method for identifying $CD3^+CD8^+$ cytotoxic T cells in a sample derived from a human, wherein said method comprises:

i) providing the sample derived from the human comprising immune cells;

ii) determining the methylation status of at least one CpG position in a genomic region for $CD8^+$ beta consisting of the sequence of SEQ ID NO: 5, wherein said determining the methylation status comprises the steps of:

a) isolating genomic DNA from said sample,

b) treating the isolated genomic DNA with bisulfite,

c) amplifying a genomic region in the bisulfite treated genomic DNA with a primer pair of SEQ ID NOs: 8 and 9 to produce an amplicon, wherein the genomic region in the bisulfite treated genomic DNA corresponds to the genomic region consisting of SEQ ID NO: 5,

d) performing a nucleic acid based assay on said amplicon to determine the methylation status of the CpG positions 40, 63, 95, 135, 142, 169, 194, 213, 216, 232, 245, 273, 339, 345, and 393 in the genomic region consisting of the sequence of SEQ ID NO: 5; and

iii) identifying the cells as $CD3^+CD8^+$ cytotoxic T cells when the CpG positions in the genomic region are methylated less than 20%.

12. The method according to claim **11**, further comprising quantifying the relative amount of said $CD3^+CD8^+$ cytotoxic T cells, said quantifying comprising detecting the methylation status of a control gene and comparing said methylation status of the control gene with the methylation status of said CpG positions in SEQ ID NOs: 5.

13. The method according to claim **11**, wherein said nucleic acid based assay is performed on a DNA-chip.

14. The method according to claim **11**, wherein said $CD3^+CD8^+$ cytotoxic T cells as identified are further distinguished from cell types selected from the group consisting of $CD19^+$ B lymphocytes, $CD15^+$ granulocytes, $CD14^+$ monocytes, $CD56^+$ natural killer Cells, $CD3^+CD56^+$ natural killer T-Cells, and $CD3^+CD4^+$ T helper cells by comparing the methylation status of the CpG positions in SEQ ID NOs: 5.

15. A method for monitoring the level of $CD3^+CD8^+$ cytotoxic T cells in a human, comprising performing the method according to claim **12**, and comparing said relative amount of said $CD3^+CD8^+$ cytotoxic T cells to a sample taken earlier or in parallel from the same human, and/or to a control sample.

16. A method for identifying $CD3^+CD8^+$ cytotoxic T cells in a sample derived from a human, wherein said method comprises:

i) providing the sample derived from the human comprising immune cells;

ii) determining the methylation status of at least one CpG position in a genomic region for $CD8^+$ beta consisting of the sequences of SEQ ID NO: 6, wherein said determining the methylation status comprises the steps of:

a) isolating genomic DNA from said sample,

b) treating the isolated genomic DNA with bisulfite,

c) amplifying a genomic region in the bisulfite treated genomic DNA with a primer pair of SEQ ID NOs: 10 and 11 to produce an amplicon, wherein the genomic region in the bisulfite treated genomic DNA corresponds to the genomic region consisting of SEQ ID NO: 6,

d) performing a nucleic acid based assay on said amplicon to determine the methylation status of the CpG positions 165, 196, 219, 267, 277, 307, 314, 341, and 410 in the genomic region consisting of the sequence of SEQ ID NO: 6; and

iii) identifying the cells as $CD3^+CD8^+$ cytotoxic T cells when the CpG positions in the genomic region are less than 20% methylated.

17. The method according to claim **16**, further comprising quantifying the relative amount of said $CD3^+CD8^+$ cytotoxic T cells, said quantifying comprising detecting the methylation status of a control gene and comparing said methylation status of the control gene with the methylation status of said CpG positions in SEQ ID NOs: 6.

18. The method according to claim **16**, wherein said nucleic acid based assay is performed on a DNA-chip.

19. The method according to claim **16**, wherein said $CD3^+CD8^+$ cytotoxic T cells as identified are further distinguished from cell types selected from the group consisting of $CD19^+$ B lymphocytes, $CD15^+$ granulocytes, CD14 monocytes, $CD56^+$ natural killer Cells, $CD3^+CD56^+$ natural killer T-Cells, and $CD3^+CD4^+$ T helper cells by comparing the methylation status of the CpG positions in SEQ ID NOs: 6.

20. A method for monitoring the level of $CD3^+CD8^+$ cytotoxic T cells in a human, comprising performing the method according to claim **17**, and comparing said relative amount of said $CD3^+CD8^+$ cytotoxic T cells to a sample taken earner or in parallel from the same human, and/or to a control sample.

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